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*Read 8/1/02*

**Combination Products Containing  
Live Cellular Components**

**Steven Boyce, PhD**

**Dept of Surgery, University of Cincinnati,  
and Shriners Burns Hospital  
Cincinnati, OH**

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**Skin Wounds**

- **Three categories:**
  - **Acute/emergent (i.e., burns, TENS)**
  - **Acute/elective (i.e., reconstruction)**
  - **Chronic/elective (i.e., ulcers)**
- **Two subcategories:**
  - **Full-thickness**
  - **Partial thickness**

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**Disease-related Risks**

- **Emergent etiology**
- **Great magnitude (>50% TBSA)**
- **Full-thickness depth**
- **Associated injury or disease**

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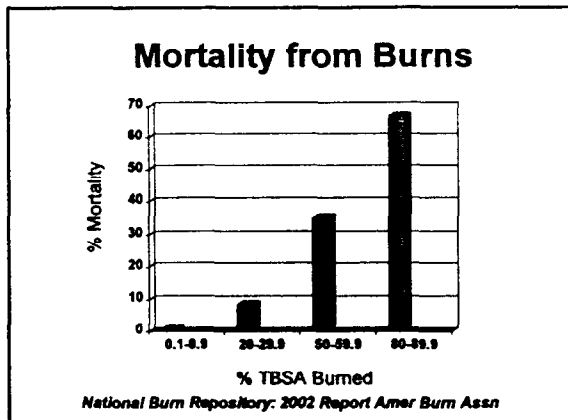
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### Human Skin: Structures & Functions

- **Three B's:**
  - **Barrier**
  - **Basement membrane**
  - **Blood supply**

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### Examples of Combination Products

| Components  | Acellular | Allogeneic                      | Autologous             |
|-------------|-----------|---------------------------------|------------------------|
| Both        | Integra™  | Apligraf™<br>Orcel™             | Cincinnati Skin Subst. |
| "Epidermis" |           |                                 | Epicel™                |
| "Dermis"    | Alloderm™ | Dermagraft™<br>(not live cells) |                        |

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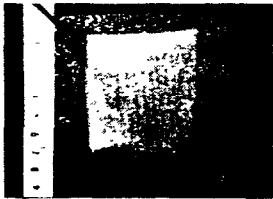

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### Composition

Cultured Skin Substitutes

- biopolymer substrate
- CSS ready for surgery
- CSS histology

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### Dermal-Epidermal Junction in CSS

Col VII

Lam 5

Native human skin

CSS

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### Cultured Skin Substitutes Do Not Blister like Epical



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### Clinical Results at 1 year




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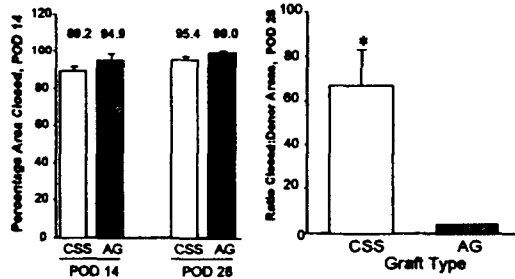
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### Engraftment and Expansion



Boyce et al, Annals of Surgery 235:269-279, 2002

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### Cultured Skin Substitutes Combined with Integra Artificial Skin



- skin is smooth, soft & strong
- usually no regrafting
- pigmentation is deficient

Boyce et al, JBCR 20:463-461, 1999

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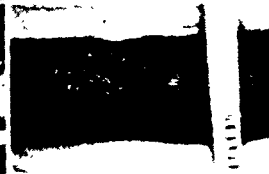
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### Burn Scar



- allograft 1 week
- graft skin substitute
- POD 11 (discharge)



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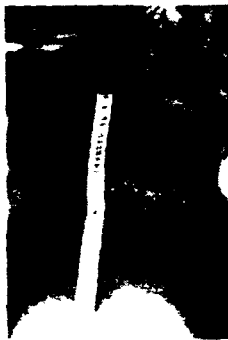
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### Giant Nevus



- risk of melanoma
- full-thickness lesion
- large body surface
- abnormal appearance

Boyce et al, JBCR 21:S222

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### Clinical Results



POD 15

POD 164

POD 366

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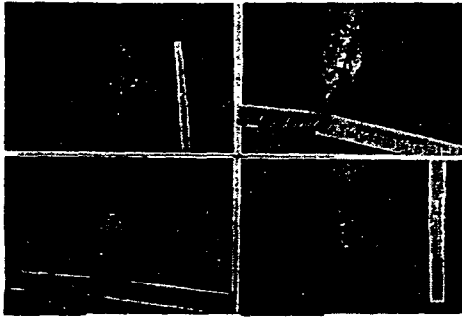
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### Clinical Results: Chronic Wounds



Boyce et al, Wounds 7:24-29, 1995

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### Efficacy: Cincinnati Skin Substitute

- Conserves donor skin
- Virtually no blistering, little regrafting
- Minimal scar
- Class III (Significant Risk) device

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### Safety: Degradable Polymeric Matrices

- CDRH-approved products:
  - Collagen
  - PGA/PLA
  - 510k approval of similar products
  - multi-center studies not mandatory
- Products without predicate:
  - Class III (Significant Risk)
  - multi-center studies required

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### Safety: Autologous Components

- Minimally Manipulated Autologous Tissue for Structural Repair ("MAS") Guidance (CBER):
  - Facilities registration
  - Processing controls
  - Multi-center studies not mandatory

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### Suggested FDA Jurisdictions

For combination products with *autologous cells*:  
Acquire tissue, process, and release as MAS under CBER.  
Matrix clearance by CDRH.  
Multi-center studies should not be mandatory.



Legend:

CBER review CDRH review

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### Safety: Allogeneic Components

- AATB Standards
  - Tissue harvest, processing & tracking
  - Microbial and viral testing
  - Facilities accreditation
- FDA (CBER) Tissue Standards
  - Donor suitability
  - Facilities registration
  - Good Tissue Practices (GTPs)
- Multi-center studies not mandatory

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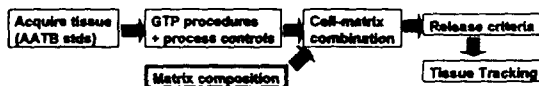
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## Suggested FDA Jurisdictions

For combination products with *allogeneic cells*:  
Acquire tissue, process, and release by AATB standards  
and GTPs under CBER. Matrix clearance by CDRH.  
Multi-center studies should not be mandatory.



Legend:

CBER review CDRH review

## Summary: combination products

- Combination products act predominantly by cellular mechanisms
- Risks from auto-combination products are less, not greater than MAS
- Risks from allo-combination products managed by AATB and GTP standards

## Conclusions: combination products

- If the primary mode of action is polymeric, then CDRH should review.
- If primary mode of action is cellular, CBER should review:
  - Products with auto cells follow MAS
  - Products with allo cells follow AATB and GTP
  - Components not typical to MAS, AATB or GTP require additional consideration
- Most combination products should not require multi-center studies, except to get claims.